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MEMORANDUM

Subject: Difenoconazole: Ecological Risk Assessment for Numerous Proposed New Uses and Changes to Registered Uses (Application Rate, Crop Groupings, and Additions to New Products)

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This memorandum summarizes the ecological risks associated with numerous proposed new uses of the fungicide difenoconazole (e.g., artichoke and ginseng). In addition, the proposed labels include application rate changes for registered uses (cucurbit), updates to crop groupings for registered uses (tree nuts and stone fruit), and the addition of registered uses to new products (e.g., ornamental and bulb vegetable). Multiple proposed use submissions are included in this risk assessment; therefore, for clarity the proposed uses and associated products are presented in **Table 2**.

Application rates and intervals are similar to previously assessed uses. The proposed single maximum application rates range from 0.07 to 0.13 lb ai/A (ground or aerial spray and chemigation). The annual maximum application rates range from 0.39 to 0.52 lb ai/(per acre for outdoor crops and per crop for indoor crops including those that can be transplanted outdoors).

Two proposed uses are assumed to have no outdoor exposure pathway and are not considered further: post-harvest treatment of pome fruit (crop group 11-10) and treatment of cucumbers in greenhouses (previously assessed at the same rate for field use). All other proposed uses have an outdoor exposure pathway including those that allow indoor treatment (e.g., greenhouse) followed by outdoor transplant. Therefore, hereinafter it is implied that references to "all proposed uses" and similar statements exclude post-harvest treatment of pome fruit and greenhouse treatment of cucumbers.

All proposed outdoor uses were assessed, including those previously registered at the same application rates because of recent updates to aquatic exposure modeling and the availability of new toxicity data. Some of these data were discussed in the last risk assessment (D409484 and D409488, 11/8/2013) and the rest were reviewed subsequent to that assessment. The recently reviewed studies address acute oral toxicity of 1,2,4-triazole, a major degradation product of difenoconazole, to bobwhite quail (MRID 49380701) and chronic toxicity of difenoconazole to mysid shrimp, a marine/estuarine invertebrate (MRID 49322901 and 49387801). Other changes include updating terrestrial invertebrate exposure estimates to reflect previously assessed application rates, assessment of risk to piscivorus birds and mammals, and consideration of an additional major degradate (CGA-205375) as identified in available fate studies. Finally, a total toxic residue (TTR) approach was used to calculate estimated environmental concentrations (EECs) due to limited availability of degradate toxicity data; this approach was not used in all previous risk assessments that considered uses that are reevaluated in the current assessment.

1. Executive Summary

The Environmental Fate and Effects Division (EFED) evaluated the proposed new uses of the systemic broad-spectrum fungicide difenoconazole. Difenoconazole is a triazole fungicide in the conazole chemical class.[1] Fungicidal activity is attributed to the inhibition of sterol biosynthesis.[2] Sterols are important for fungi membrane structure and function.

A number of risk assessments have been conducted on difenoconazole. Previous assessments identified risk concerns primarily for aquatic invertebrates, fish, birds, and mammals on a chronic basis and on an acute basis for estuarine/marine invertebrates for certain uses. Risk concerns for terrestrial plants were limited to listed dicot species. Taxonomic groups for which concern levels were exceeded for the proposed uses (**Table 1)** are similar to those identified in previous assessments. The risk concerns apply to all proposed uses.

Table 1. Potential Effects to Listed Species Associated with All of the Proposed New Uses of Difenoconazole[1]

Listed Taxa	Direct Effects	Indirect Effects
Terrestrial and semi-aquatic plants – monocots and dicots	Yes (listed dicots)	Yes
Birds	No – Acute Yes – Chronic	Yes

[1] http://www.alanwood.net/pesticides/class_fungicides.html
[2] http://www.frac.info/frac/publication/anhang/2014%20FRAC%20Code%20List.pdf

Listed Taxa	Direct Effects	Indirect Effects
Terrestrial-phase amphibians	No – Acute Yes – Chronic	Yes
Reptiles	No – Acute Yes – Chronic	Yes
Mammals	No – Acute Yes – Chronic	Yes
Aquatic plants	No[2]	Yes
Freshwater fish	No – Acute Yes – Chronic	Yes
Aquatic-phase amphibians	No – Acute Yes – Chronic	Yes
Freshwater invertebrates	No – Acute Yes – Chronic	Yes
Estuarine/marine fish	No – Acute Yes – Chronic	Yes
Estuarine/marine invertebrates	Yes – Acute Yes – Chronic	Yes
Terrestrial invertebrates	No	Yes[3]

[1] Risk concerns are applicable to all proposed uses except post-harvest treatment of pome fruit and greenhouse treatment of cucumber.
[2] There is some uncertainty for non-vascular plants because an acceptable study with cyanobacteria is not available; however, there are not currently any listed non-vascular plant species.
[3] Only for obligate relationships with listed terrestrial plant species (dicots).

2. Data Gaps

This assessment, like previous risk assessments, did not identify an acute contact risk concern for honeybees. However, given that exposure is expected and that difenoconazole is systemic, the following studies are now recommended based on the current guidance for pollinator risk assessment (USEPA, 2014).

- Special study (OECD 213): Acute oral toxicity to adult honeybees – difenoconazole (TGAI)
- Special study: Chronic oral toxicity to adult honeybees – difenoconazole (TGAI)
- Special study: Chronic and acute toxicity to larval honeybees (acute value can be obtained simultaneously with chronic study) – difenoconazole (TGAI)

Several data gaps remain, as identified in past risk assessments (data unavailable or available data are insufficient). The impact of these data gaps on the risk conclusions varies with the use and application rate of difenoconazole.

- 850.2100 (Acute oral toxicity to birds) – CGA-142856 (i.e., triazole acetic acid)

- 850.4550 (Cyanobacteria toxicity) – difenoconazole (TGAI)

- 850.4100 (Terrestrial plant toxicity, seedling emergence) – TEP
  - The available Tier I study is supplemental because there were biologically significant effects observed in dicots at the limit test concentration which is below the maximum labeled single application rate (turf; 0.26 lb ai/A). The current risk assessment is impacted by the lack of a NOAEC for dicots. Tier II testing is required for the dicot species that showed effects in the available study (lettuce, soybean, and sugar beet). Furthermore, a NOAEC must be established at the maximum single application rate (Tier 1 test) for the other seven test species (those showing no effects in the available study) to meet the data requirement; alternatively, Tier II testing may be conducted for those species.

- 850.4150 (Terrestrial plant toxicity, vegetative vigor) – TEP
  - The available Tier I study is supplemental because the limit test concentration is below the maximum labeled single application rate (turf; 0.26 lb ai/A). The current risk assessment is not impacted. To meet the data requirement, a NOAEC must be established for all ten test species at the maximum single application rate (Tier I test). Alternatively, Tier II testing may be conducted.

- Chronic toxicity to benthic invertebrates (whole sediment: freshwater and estuarine/marine) – difenoconazole (TGAI)
  - There is uncertainty associated with chronic risk to benthic invertebrates given that pore water EECs are similar to water column EECs and a lack of acceptable toxicity data for benthic invertebrates. Although a sediment toxicity study (range finding with a freshwater midge) is available, the numerous deviations in the study limit its use for quantitative purposes. Data are recommended in part because the chronic LOC (1.0) is exceeded for aquatic invertebrates based on comparison of water column species toxicity data to pore water EECs. Sediment chronic toxicity testing with three species is recommended: freshwater midge, freshwater amphipod, and marine/estuarine amphipod.

In addition, submission of chronic toxicity data (1,2,4-triazole, triazole acetic acid, and CGA-205375) may be useful for refining the risk concerns for birds, fish, and aquatic invertebrates.

3. Uncertainties

3.1 General

- The assessment of chronic risk to benthic invertebrates was based on toxicity to water column species due to a lack of data suitable for quantitative risk assessment. Risk conclusions for the proposed uses are the same for benthic invertebrates because the pore water EECs are similar to water column EECs; that is, there is a chronic risk concern for benthic invertebrates. The risk concern for water column species is protective of benthic species in general (i.e., there is a risk concern); however, risk may be over or underestimated and the magnitude of the RQ associated with that concern is uncertain without toxicity data.

- There is some uncertainty about risk to aquatic plants because an acceptable study with blue green algae (cyanobacteria) is not available. There are not currently any listed non-vascular plants so the uncertainty is for non-listed species. Blue-green algae would need to be about 6-9 times more sensitive than *Navicula pelliculosa* to exceed the LOC (non-listed species).

- Because it is persistent, difenoconazole and its degradates may accumulate in soil after repeated use. This repeated or continuous exposure may result in significant risks to non-target organisms, especially birds and mammals. Furthermore, given that difenoconazole is also systemic, surface residues may underestimate exposure to terrestrial animals and underestimate risk.

- This assessment assumes that EECs for outdoor uses are representative of EECs for indoor treated plants that may be transplanted outdoors. Based on this assumption, risk to terrestrial plants (from runoff only), aquatic organisms, and piscivorus animals from use on transplants is likely overestimated (e.g., there is no spray drift from transplants) but may be underestimated in some cases. Risk from use on transplants will be from runoff only and will depend on many factors including but not limited to the density of plants once moved outdoors, the soil matrix, the duration that treated plants remain in a given location (e.g., at a store, at a residence, etc.), and the location of the plant (e.g., unplanted vs. planted).

- This risk assessment only considered the most sensitive of the species evaluated in the registrant-submitted studies. The position of the tested species relative to the distribution of all species' sensitivities to difenoconazole is unknown. Extrapolating the risk conclusions from the most sensitive tested species to non-tested species may either underestimate or overestimate the potential risks to those species.

- Several of the assessed products are mixed with another active ingredient. This assessment only addresses risk from difenoconazole alone and the other active ingredients will be assessed separately. In addition, this assessment does not address possible interactions among the active ingredients that may impact the toxicity of difenoconazole.

3.2 Labels

- Annual application rates (maximum lb ai/A/year) were provided for all proposed outdoor uses. However, some of the same uses have rates on a per season basis on the labels of previously registered products. For example, the proposed Alibi Flora label states a limit of 0.46 lb ai/A/year for Brassica (cole) leafy vegetable use whereas existing product labels (e.g., Inspire, Inspire, Quadris Top) state a limit of 0.46 lb ai/A/season for the same use. The annual limits reduce uncertainty in potential exposure because difenoconazole is persistent. **EFED recommends updating all relevant product labels with the annual application limits for all uses considered in this assessment.**

- Changes to the proposed labels were previously agreed upon with the registrant. The risk assessment reflects the following anticipated changes to the Inspire Super label which are outstanding at this time and should be addressed:

    - <u>Stone fruit, crop group 12-12</u>: Specific use instructions should be changed from "Do not apply more than 0.46 lb ai/A of difenoconazole-containing product per crop per year" to "Do not apply more than 0.46 lb ai/A of difenoconazole-containing product per year".
    - <u>Berry and small fruit; bushberry subgroup 13-07B</u>: Specific use instructions should be changed from "Do not apply more than 28 fl. oz. of Inspire Super per crop per year" to "Do not apply more than 80 fl. oz. of Inspire Super per crop per year".

4. Summary of Proposed Uses

Numerous uses are proposed with application rates and intervals that are similar to previously assessed uses (**Table 2**). The proposed single maximum application rates range from 0.07 to 0.13 lb ai/A (ground or aerial spray and chemigation). The annual maximum application rates range from 0.39 to 0.52 lb ai/(per acre for outdoor crops and per crop for indoor crops including those that can be transplanted outdoors).

Two proposed uses are assumed to have no outdoor exposure pathway and are not considered further: post-harvest treatment of pome fruit (crop group 11-10) and treatment of cucumbers in greenhouses (previously assessed at the same rate for field use).

Several uses on the proposed Alibi Flora label may be applied by ground or chemigation methods; however, aerial applications are allowed for those same uses on other labels (Inspire, Inspire Super, and Quadris Top; *see Comments in* **Table 2**). Aerial application methods were modeled in this assessment because they typically result in higher EECs than ground application methods and modeling procedures have changed since the uses were previously assessed for aerial application.

Table 2. Proposed Uses for Difenoconazole

Proposed Use	Maximum Application Rate Minimum Application Interval[1] Application Method	End Use Products	DP	Comments
Artichoke[2]	0.115 lb ai/A x 4 applications (14 day interval) 0.46 lb ai/A/year of difenoconazole containing products Air, ground, and chemigation A different mode of action fungicide should be alternated after two sequential applications.	Inspire, Inspire Super, Quadris Top	421513 421518 421519 421523	

Proposed Use	Maximum Application Rate Minimum Application Interval[1] Application Method	End Use Products	DP	Comments
Ginseng[2]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year of difenoconazole containing products Air, ground, and chemigation A different mode of action fungicide should be alternated after two sequential applications.	Inspire, Quadris Top	421518 421519 421523	
Tree Nuts (Crop group 14-12)[2]	0.115 lb ai/A x 4 applications (14 day interval) 0.46 lb ai/A/year Air and ground A different mode of action fungicide should be alternated after two sequential applications.	Inspire, Quadris Top	421518 421519 421523	Registered use updated to crop group 14-12.
Stone Fruit (Crop group 12-12)[2]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year of difenoconazole containing products Air and ground	Inspire, Inspire Super, Quadris Top	421518 421519 421523	Registered use updated to crop group 12-12.
Greenhouse cucumber	0.114 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/season of difenoconazole containing products A different mode of action fungicide should be alternated after two sequential applications.	Inspire Super	421513 421523	
Pome fruit (Crop group 11-10)	Post harvest treatment (dip, drench, flood, or spray)	Academy	417610	
Berry and small fruit; bushberry subgroup 13-07B[2]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year of difenoconazole containing products Air and ground A different mode of action fungicide should be alternated after two sequential applications.	Inspire, Inspire Super, Inspire XT, Quadris Top	418502	

Proposed Use	Maximum Application Rate Minimum Application Interval[1] Application Method	End Use Products	DP	Comments
Legume vegetables; dried shelled pea and bean (except soybean) subgroup 6C[2]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year of difenoconazole containing products Air, ground, and chemigation A different mode of action fungicide should be alternated after two sequential applications.	Inspire, Inspire Super, Inspire XT, Quadris Top	418502	
Ornamentals[3]	0.13 lb ai/A x 4 applications (7 day interval) 0.52 lb ai/A/year (outdoor) or /crop (indoor)[4] Air, ground, and chemigation Alternate with another fungicide after 2 or 3 applications depending on the disease.	Alibi Flora	418014	*Registered on:* Inspire (1/9/2013 version) 0.13 lb ai/A x 4 applications (7 day interval); 0.52 lb ai/A/year; application method not stated: assumed air, ground, chemigation; alternation with another fungicide is not required
Brassica (Cole) Leafy Vegetables[2,3]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year (outdoor) or /crop (indoor)[4] Ground and chemigation Alternate with another fungicide after one application.	Alibi Flora	418014	*Registered on:* Inspire (1/9/2013 version) & Inspire Super (8/30/2012 version) 0.114 lb ai/A x 4 applications (7 day interval); 0.46 lb ai/A/season; air, ground, chemigation; rotate fungicides after 2 sequential applications Quadris Top (11/20/2013 version) 0.115 lb ai/A x 4 applications (7 day interval); 0.46 lb ai/A/season; air, ground, chemigation; rotate fungicides after 1 application
Bulb Vegetables[2,3]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year (outdoor) or /crop (indoor)[4] Ground and chemigation Alternate with another fungicide after one application. * Green onions are limited to 3 applications or 0.345 lb ai/A/year (outdoor) or /crop (indoor)	Alibi Flora	418014	*Registered on:* Inspire (1/9/2013 version) & Inspire Super (8/30/2012 version) & Inspire XT (8/2/2012 version) 0.114 lb ai/A x 4 applications (7 day interval); 0.46 lb ai/A/season; air, ground, chemigation; rotate fungicides after 2 sequential applications Green onions limited to 3 applications (0.34 lb ai/A/season) Quadris Top (11/20/2013 version) 0.115 lb ai/A x 4 applications (7 day interval); 0.46 lb ai/A/season; air, ground, chemigation; rotate fungicides after 1 application

Proposed Use	Maximum Application Rate Minimum Application Interval[1] Application Method	End Use Products	DP	Comments
Cucurbit Vegetables[2]	0.115 lb ai/A x 4 applications (7 day interval) 0.46 lb ai/A/year (outdoor) or /crop (indoor)[4] Ground and chemigation Alternate with another fungicide after one application. --- 0.114 lb ai/A x 4 applications + 0.064 lb ai/A x 1 application (7 day interval) 0.52 lb ai/A/year of difenoconazole containing products Air, ground, and chemigation A different mode of action fungicide should be alternated after two sequential applications.	Alibi Flora ------------- Inspire Super	418014 --------- 421513 421523	Proposed annual application rate for Inspire Super is higher than registered rate for this use.
Fruiting Vegetables (except tomato)[2,3]	0.113 lb ai/A x 4 applications (7 day interval) 0.45 lb ai/A/year (outdoor) or /crop (indoor)[4] Ground and chemigation Alternate with another fungicide after two applications.	Alibi Flora	418014	*Registered on:* Inspire (1/9/2013 version) & Inspire Super (8/30/2012 version) 0.114 lb ai/A x 4 applications (7 day interval); 0.46 lb ai/A/season; air, ground, chemigation; rotate fungicides after 2 sequential applications; includes tomato Quadris Top (11/20/2013 version) 0.115 lb ai/A x 4 applications (7 day interval); 0.46 lb ai/A/season; air, ground; rotate fungicides after 2 sequential applications; excludes tomato
Tomato[3]	0.0656 lb ai/A x 6 applications (7 day interval) 0.385 lb ai/A/year (outdoor) or /crop (indoor)[4] Ground and chemigation Alternate with another fungicide after two applications.	Alibi Flora	418014	*Registered on:* Quadris Top (11/20/2013 version) 0.0656 lb ai/A x 7 applications (7 day interval); 0.46 lb ai/A/season; air, ground, chemigation; rotate fungicides after 2 sequential applications

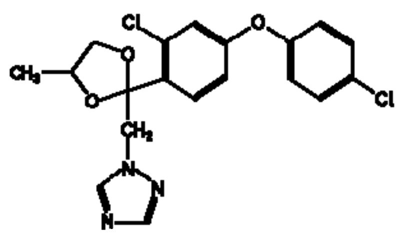
[1] Some uses require alternating to another fungicide between applications of difenoconazole-containing products. The labels do not specify an application interval between non-sequential difenoconazole applications. In those cases an additional 7 days was added to the labeled minimum application interval for modeling purposes. For example, if the minimum application interval is 14 days and two sequential applications are permitted then a 21 day interval was assumed between the 2nd and 3rd difenoconazole application.
[2] Single application rates for individual products range from 0.114-0.115 lb ai/A
[3] Use is registered on other labels (Inspire, Inspire Super, and Quadris Top) at the same or higher application rates for aerial application methods. Although not on the proposed Alibi Flora label, aerial application methods were modeled in this assessment because aerial application methods typically result in higher EECs than ground application methods and modeling procedures have changed since the same use was assessed for aerial

application. In addition, labels differ in terms of the permitted number of sequential applications of difenoconazole. The aerial application with the overall shortest interval period was considered for modeling purposes (i.e., the period between the first and final application). For example, four sequential applications at 7 day intervals has an overall interval period of 21 days whereas 4 applications with variable intervals of 7 days (between 1st and 2nd application), 14 days (2nd and 3rd), and 7 days (3rd and 4th) due to alternating to another fungicide between the 2nd and 3rd difenoconazole application has an overall interval period of 28 days.
[4] Indoor treated plants may be transplanted outdoors (Alibi Flora label).

5. Fate and Transport Summary

Based on a low vapor pressure of 2.5 x 10^{-10} mm Hg and solubility in water of 15 mg/L, difenoconazole has a low propensity to volatilize and generate vapors after application. At test termination in laboratory studies, the residues detected in an organic volatiles trap totaled 0.7% or less; most instances were less than 0.1% of the applied difenoconazole. The concentrations of the applied difenoconazole lost through volatilization were not measured in the terrestrial field dissipation studies. Selected physical and chemical properties are presented in **Table 3**.

Table 3. Physical and Chemical Properties of Difenoconazole

Property	Value	Source
Common Name	Difenoconazole	MRID 46950104
CAS Registry No.	119446-68-3	
PC Code	128847	
Structure		MRID 46950104
Chemical Name (CAS)	1-{2-[4-(chlorophenoxy)-2-chlorophenyl-(4-methyl -1,3-dioxolan-2-yl)-methyl]} -1H-1,2,4-triazole	MRID 46950104
SMILES notation	O1CC(C)OC1(Cn2ncnc2)c3c(Cl)cc(Oc4ccc(Cl)cc4)cc3	EPI Suite, v3.12 SMILES
Molecular Formula	$C_{19}H_{17}Cl_2N_3O_3$	MRID 46950104
Molecular Weight	406.27	MRID 46950104
Physical State	Red Liquid	
Vapor pressure	2.5 x 10^{-10} mm Hg (25 ^oC)	MRID 46515901
Henry's Law constant	8.9 x 10^{-12} atm x m^3/mol	MRID 46515901
Specific Gravity/ Density	1.14g/cm^3 @ 25 ^oC	MRID 46950104
Solubility in water	15.0 mg/L @ 25 ^oC	MRID 46950104

Property	Value	Source
log K_{ow}	4.4 (25 °C)	MRID 46950105

In soil, difenoconazole is persistent and slightly mobile. Difenoconazole has a low potential to reach groundwater, except in soils of high sand and low organic matter content. During a runoff event, difenoconazole will potentially enter adjacent bodies of surface water. In an aquatic environment, difenoconazole's main route of dissipation is partitioning into the bottom sediment as shown in an aerobic aquatic metabolism study (MRID 42245134), in which the distribution ratio of sediment and water phases was 8:1 at 1 day post-treatment and 40:1 at 30 days post-treatment. Difenoconazole has the potential to undergo slow to relatively fast aqueous photolysis in clear water. **Table 4** summarizes the environmental fate data of difenoconazole. Additional environmental fate data, including major degradates and maximum percent formation can be found in a previous assessment (DP377719, 7/2010).

Table 4. Summary of the Environmental Fate Properties of Difenoconazole

Property	Value	Source
Name	Difenoconazole	
Henry's Law constant	8.9×10^{-12} atm x m^3/mol	MRID 46515901
Soil adsorption coefficient K_{oc} (L/kg)	3867, 3518, 3471, and 7734 3870, 4587, 4799, and 11202	MRID 42245135 [1] MRID 46950121
Hydrolysis half-life pH = 5 pH = 7 pH = 9	 Stable Stable Stable	 MRID 42245127
Photolysis half-life in water	6 days – ca. 1 ppm in sterile buffer solution (30-day study) ca. 9.2 days – 1mg ai/L in natural water 228 days – 1.52 ml ai/L in sterile buffer solution (15-day study)	MRID 42245128 MRID 46950104 MRID 46950105[2]
Photolysis half-life in soil	349 - 823 days	MRID 46950106[3]
Aerobic soil metabolism half-life	84.5 days – at 0.1 ppm concentration 1600 days – at 10 ppm in loam 1059 days – at 10 ppm in sandy loam 120 days – at 0.13 ppm; Swiss loam 104 days – at 0.13 ppm; Swiss loam 165 (158) days – at 0.23 ppm; Swiss sandy loam 204 (187) days – at 0.23 ppm; Swiss sandy loam/loamy sand 204 (198) days – at 0.23 ppm; French silty clay loam 433 (408) days – at ca. 0.1 ppm in CA loamy sand at 25 °C 533 days – at ca. 0.1 ppm in CA loamy sand at 25 °C	MRID 42245131 MRID 42245132[4] MRID 42245133[4] MRID 46950109 MRID 46950110 MRID 46950111 MRID 46950112 MRID 46950114
Anaerobic soil metabolism half-life	947 days – at 10 ppm in loam	MRID 42245132

Property	Value	Source
Aerobic aquatic metabolism half-life	860 days (10 mg ai/L) 315 (330) days (nominal 0.1 kg ai/ha =0.17 mg ai/L); Swiss pond water-silty clay loam sediment) 335 (301) days (0.17 mg ai/L; Swiss river water-sandy loam sediment) 565 days (0.04 mg ai/L)	MRID 42245134 [5] MRID 46950116 MRID 46950117
Anaerobic aquatic metabolism half-life	1245 days (10 mg ai/L) 370 days (433) (0.04 mg ai/L)	MRID 42245134 [5] MRID 46950119
Terrestrial field dissipation half-life	252 days - determined in the 0- to 3-inch depth – CA bare loamy sand 231 days – GA bare loamy sand (four applications of 0.13 lb ai/A) 139 days – CA bare plot of loam soil (four applications of 0.13 lb ai/A) 462 days – ND bare sandy clay loam	MRID 42245140 MRID 46950126 MRID 46950127 MRID 46950129
Laboratory accumulation in bluegill sunfish bioaccumulation factor (*Lepomis macrochirus*) Depuration half-life	170x in edible tissues 570x nonedible tissues 330x for whole body 1 day	MRID 42245142

[1] There was another adsorption/desorption study (MRID 42245136) reviewed in which the test soils were autoclaved prior to conducting the study which could distort the mobility characteristic of difenoconazole, thus, the study results were not used for calculation of modeling input parameters.
[2] For modeling purposes, the longest half-life was used as it represents the most conservative scenario. However, there is considerable uncertainty in the photolysis half-lives because the duration of the studies was considerably shorter than the extrapolated half-life (MRIDs 46950105 and 46950106).
[3] The soil photolysis half-life under xenon light condition was recalculated to represent the conditions under natural sunlight intensity during 30-day periods between June and September (104.7-246.9 W·min/cm^2), as a result, a range of half-lives was obtained.
[4] The test application rate was significantly higher than expected under registrant-proposed use conditions for difenoconazole (MRID 42245132 and MRID 42245133).
[5] In aquatic metabolism studies, the test application rates were significantly higher than expected under registrant-proposed use conditions for difenoconazole.

6. Exposure Summary

Exposure was considered for the proposed outdoor uses and the indoor uses that allow outdoor transplant.

6.1 Terrestrial Exposure

Difenoconazole surface-residue EECs for birds and mammals were not calculated because the proposed applications rates for outdoor uses and indoor uses allowing for outdoor transplant are the same as those associated with previously assessed uses.[3,4]

[3] Previous assessments (see DP333319 and DP340041, 7/2007; DP361251, 8/2009; DP378927 and DP384047, 2/2011) reported the maximum single application rate as 0.114 lb ai/A. The rate on some labels (e.g., Quadris Top) is 0.115 lb ai/A (0.1148 lb ai/A); however, this small difference (<1%) does not change risk conclusions.
[4] The registrant proposed increasing the outdoor application rate for cucurbit vegetables only on the Inspire Super label (previously assessed rate was 0.114 lb ai/A x 4 applications at a 7 day interval for a seasonal maximum of 0.456 lb ai/A; proposed rate is 0.114 lb ai/A x 4 applications plus 0.064 lb ai/A x 1 application at a 7 day interval for

Previous risk assessments did not assess exposure to 1,2,4-triazole, triazole acetic acid, or CGA-205375.[5] The current assessment considers risk from these degradates based on available toxicity data. T-REX (Terrestrial Residue Exposure Model, v 1.5.2)[6] was used to estimate avian and mammal surface-residue exposure. Representative input parameters and EECs are shown in **Appendix A**.

Risk to piscivorus animals was not considered in previous risk assessments. The current assessment used KABAM (KOW (based) Aquatic BioAccumulation Model, v 1.0)[7] to estimate potential bioaccumulation of difenoconazole in freshwater aquatic food webs and risk to piscivorus mammals and birds that consume difenoconazole contaminated fish. Bioaccumulation was based on surface water TTR EECs because the log Kow of difenoconazole (4.4) and CGA-205375 (3.79; EPISUITE estimate) suggest the potential for bioaccumulation of both compounds in the aquatic food web. Furthermore, CGA-205375 was observed in fish tissue (51%-64% of applied difenoconazole) in the available BCF study. Use of TTR EECs may overestimate exposure to piscivorus animals because they include contributions from other major degradates (1,2,4-triazole and triazole acetic acid) which have low bioaccumulation potential based on their log Kow values (-0.76 and -1.71, respectively; EPISUITE estimate). The method used to generate TTR EECs (GENEEC) for surface water does not provide EECs for pore water. For modeling purposes, pore water TTR EECs were assumed equal to surface water TTR EECs given the relatively small difference in surface water and pore water EECs based on difenoconazole alone (**Appendix D**, **Table D-1 and D-2**).[8] Representative KABAM input parameters and EECs are presented in **Appendix B**.

Tier 1 EECs were calculated for honeybees because risk to bees was not previously assessed for some of the proposed application rates (the guidance to assess pesticide risk to bees was only recently approved; USEPA, 2014). The acute contact EEC for the highest proposed single application rate is calculated as follows:

$$\text{Acute contact EEC} = 0.13 \text{ lb ai/A} * 2.7\ \mu\text{g ai/bee per lb ai/A} = 0.351\ \mu\text{g ai/bee}$$

TerrPlant (v 1.2.2)[6] was used to calculate EECs for characterizing exposure to terrestrial and semi-aquatic plants through spray drift and run-off of difenoconazole. EECs were not previously calculated for the proposed application rates because acceptable toxicity data were not available

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an annual maximum of 0.52 lb ai/A). This annual application rate is equal to the previously assessed seasonal rate for turf and ornamentals; however, the single application rates, application intervals, and numbers of applications differ. Therefore, EECs are presented in **Appendix A** to demonstrate that exposure and risk for the proposed increased application rate for cucurbit vegetables (Inspire Super label only) is covered by previously assessed uses.

[5] The exception is uses with a single application; EECs for single application uses include potential formation of degradates. In this case risk conclusions would not change unless any degradates are substantially more toxic than difenoconazole (see risk assessment for use on canola, 11/2013, DP 409484 and 409488).

[6] www.epa.gov/oppefed1/models/terrestrial

[7] www.epa.gov/oppefed1/models/water

[8] CGA-205375 may or may not have similar pore water and surface water concentrations. Nonetheless, pore water concentrations had negligible effect on dose-based and dietary-based EECs calculated in KABAM. A sensitivity analysis indicates that there is less than 5% difference between KABAM EECs calculated (1) assuming pore water TTR EECs = surface water TTR EECs and those calculated (2) using pore water EECs based on difenoconazole only (lower end estimate that does not account for CGA-205375, **Table D-2**) and surface water TTR EECs.

when past risk assessments considered risk from the same application rates. Input and output for the maximum proposed single application rate (ornamentals) are presented in **Appendix C**.

6.2 Aquatic Exposure

TTR EECs were used to characterize risk to aquatic organisms due to a partial or complete lack of toxicity data for each major degradate (1,2,4-triazole, triazole acetic acid, and CGA-205375). Difenoconazole-only EECs were used to further characterize risk.

It was assumed that degradates and difenoconazole are equally as toxic to all aquatic organisms for TTR EEC analysis. The GENEEC model is unable to generate TTR EECs based on a subset of specific degradates of potential toxicological concern. Therefore, due to a lack of CGA-205375 toxicity data, two of the major degradates (1,2,4-triazole and triazole acetic acid) are also assumed equally as toxic as difenoconazole on an acute basis for modeling purposes even though data indicate reduced acute toxicity of those degradates to freshwater fish and invertebrates compared to difenoconazole. Nonetheless, there is no impact on risk conclusions for acute risk to fish and invertebrates despite this assumption due to modeling limitations.

6.2.1 Exposure Estimates for Difenoconazole

The Surface Water Concentration Calculator (SWCC v 1.106) model[9] was used to generate EECs for the Tier II aquatic exposure assessment. The SWCC is a graphical user interface that runs the Pesticide Root Zone Model (PRZM, v 5) and the Variable Volume Water Body Model (VVWM). Simulations are run for multiple (usually 30) years and the EECs represent peak values that are expected once every ten years based on the thirty years of daily values generated during the simulation.

The SWCC input parameters for difenoconazole are shown in **Table 5**. Difenoconazole-only EECs (surface water and pore water) are presented in **Appendix D** and a representative SWCC output is presented in **Appendix E**.

Table 5. Chemical Specific SWCC Model Input Parameters for Difenoconazole

Parameter	Input Value and Unit	Source/Comments
Crops	**Scenario**	
Artichoke	CArowcrop RLF	Surrogate scenario
Ginseng	MNsugarbeetSTD	Surrogate scenario
Bushberry	ORberriesOP and NYgrapeSTD	Surrogate scenarios
Legumes	MIbeanSTD and WAbeanNMC	Standard and surrogate scenarios
Cucurbit	FLcucumberSTD and CAMelonRLF	Standard and surrogate scenarios
Fruiting vegetables	FLpeppersSTD and PAtoamtoSTD	Standard and surrogate scenarios
Bulb vegetables	GAonionSTD and CAonionSTD	Standard scenarios
Brassica (Cole) Leafy vegetables	CALettuceSTD and FLCabbageSTD	Standard scenarios
Tree nut	CAalmondSTD, GApecanSTD and ORfilbertsSTD	Standard scenarios

[9] www.epa.gov/oppefed1/models/water

Parameter	Input Value and Unit	Source/Comments
Stone Fruits Ornamentals	GApeachesSTD and MIcherriesSTD CAnurserySTD_V2 FLnurserySTD_V2 MInurserySTD_V2 ORnurserySTD_V2, and TNnurserySTD_V2	Standard scenarios Standard scenarios
Maximum single application rate x Maximum # of application Artichoke, ginseng, bushberry, legume, fruiting vegetables, bulb vegetables, brassica (cole) leafy vegetables, tree nuts, and stone fruit Ornamental Cucurbit	 0.115 lb ai/A (0.129 kg ai/HA) x 4 0.113 lb ai/A (0.128 kg ai/HA) x 4 0.114 lb ai/A (0.128 kg ai/HA) x 4 and 0.064 lb ai/A (0.072 kg ai/HA) x 1	 EPA Reg. No. 100-1262 EPA Reg. No. 100-1312 EPA Reg. No. 100-1313 EPA Reg. No. 100-1317 EPA Reg. No. 100-1262 EPA Reg. 100-1317
Method of application CAM = 2	Foliar Spray	Product Label as above
Application efficiency	0.99 (Ground Spray) 0.95 (Aerial Spray)	No chemigation scenario was modeled but assumed similar to ground application. EFED Model Input Guidance, Version 2.1 (USEPA, 2009)
Spray drift	0.062 (Ground Spray) 0.125 (Aerial Spray)	USEPA, 2013
Crop Scenario: Application date and minimum interval between applications (days)	**Artichoke** CArowcrop: June 9 (14)	Assumed 21-days for application intervals between 2nd and 3rd
	Ginseng MNsugarbeet: Sept 17 (7)	Assumed 14-days for application intervals between 2nd and 3rd
	Busherry ORberries: June 19 (7) NYgrape: Sept 10 (7)	Assumed 14-days for application intervals between 2nd and 3rd
	Legume MIbeanSTD: July 03 (7) WAbeanNMC: July 01 (7)	Assumed 14-days for application intervals between 2nd and 3rd
	Cucurbit FLcucumber: Oct 22 (7) CAmelon: June 14 (7)	Assumed 14-days for application intervals between 2nd and 3rd and 4th and 5th
	Fruiting Vegetables FLpeppers: Oct 27(7) PATomato: Sept 10 (7)	Assumed 14-days for application intervals between 2nd and 3rd
	Bulb vegetables CAonion: July 11(7) GAonion: July 11 (7)	Assumed 14-days for application intervals between 2nd and 3rd

Parameter	Input Value and Unit	Source/Comments
	Brassica (Cole) leafy Vegetables CAlettuce: Apr 07 (7) FLcabbage: Jan 11 (7)	Assumed 14-days for application intervals between 2nd and 3rd
	Tree nuts CAalmonds: Jul 12 (14) GApecans: Aug 10 (14) ORfilberts: Aug 09 (14)	Assumed 21-days for application intervals between 2nd and 3rd
	Stone Fruits GApeaches: Aug 10 (7) MIcherries: Jun 30 (7)	---
	Ornamentals CAnursery: Jun 01 FLnursery: Jun 01 MInursery: Jun 01 ORnursery: Jun 01 TNnursery: Jun 01	Assumed late spring
Hydrolysis	Stable	MRID 42245127
Aerobic soil metabolism ($t_{1/2}$)[1]	313 days	MRID 42245131, 4695010912, and 46950114
Aerobic aquatic metabolism ($t_{1/2}$)[2]	556 days	MRID 46950116 and 46950117
Anaerobic aquatic metabolism ($t_{1/2}$)[3]	1110 days	MRID 46950119
Aquatic photolysis $t_{1/2}$ (days)[4]	Stable	MRID 46950105
Vapor pressure	2.5×10^{-10} mm Hg (25 ^{o}C)	MRID 46515901
Solubility in water	15 mg/L (25 ^{o}C)	MRID 46515901
Molecular Weight	406.27	MRID 46950104
Partition coefficient K_{oc}	5381 mL/g	MRID 42245135 and 46950121

[1] The 90% of the UCL of the mean metabolism half-life.
[2] The 90% of the UCL of the mean metabolism half-life of all available half-lives but those obtained for high test rate.
[3] At proposed application rate only one half-life was available; thus, the half-life was multiplied by three (i.e., 3 x 370 days).
[4] Estimated half-life is beyond the duration of study thus, considered stable.

6.2.2 Exposure Estimates for the Total Toxic Residues of Difenoconazole

Difenoconazole and its major degradates (1,2,4-triazole, triazole acetic acid, and CGA-205375), are assumed to be persistent in the environment with a low soil partition coefficient in all modeled media. In general, for persistent chemicals, yearly EECs of PRZM/VVWM are not independent and are correlated to the previous year's concentration in PRZM/VVWM output. Therefore, the GENEEC model was used to estimate EECs for TTR (difenoconazole + 1,2,4-triazole + triazole acetic acid + CGA-205375) to characterize potential effects on aquatic organisms. For the TTR GENEEC modeling, all input parameters were the same as listed in **Table 5** with the exception of the photolysis half-life, the aerobic soil metabolism half-life, and the aerobic and anaerobic aquatic metabolism half-lives which were assumed to be zero (stable). A soil partition coefficient (Koc) of 1000 mg/L was also assumed for the total toxic residues. The TTR EECs for the proposed uses are presented in **Appendix D** and a representative GENEEC output file is presented in **Appendix F**.

6.2.3 Monitoring Data

Monitoring data for difenoconazole were available from the United States Geological Survey

(USGS) National Water-Quality Assessment (NAWQA) Program Data Warehouse[10], searched on November 06, 2014. Difenoconazole was detected in only one of seventy two surface water samples from multiple states (CA, GA, IA, IN, MO, NE, and WI); the reported maximum concentration (18.2 ng/L) was detected in California. Difenoconazole was not detected at the limits of quantitation (LOQ) of 0.6 and 1.0 µg/kg-sediment in any of the 83 sediment samples collected from multiple states (GA, IA, IN, KS, KY, MO, NE, OH, SD, and WI). However, the study design of NAWQA is not targeted to account for all difenoconazole use areas, timing of application, and other factors which may more accurately represent spatially and temporally dependent variables influencing runoff vulnerability. No groundwater data are available at this time.

Monitoring data for surface water, groundwater, and sediment from the California Department of Pesticide Regulation (CDPR)[11] were searched on November 06, 2014. No monitoring data were available for difenoconazole on CDPR's website.

7. Ecological Effects Summary

Toxicity data are summarized in **Tables 6 to 12** (for details see DP377719, 7/2010 and DP409484 and DP409488, 11/2013). Two toxicity studies have been reviewed since the last risk assessment: mysid full life-cycle (TGAI; MRID 49322901 and 49387801) and northern bobwhite quail oral toxicity (1,2,4-triazole; MRID 49380701). These studies are briefly summarized below and are incorporated into this risk assessment. In addition, a 1,2,4-triazole toxicity study with freshwater algae (MRID 45880401) is in review.

The recently submitted mysid full life-cycle study (TGAI; MRID 49322901 and 49387801) showed effects on F0 post-pairing survival, offspring/female, and time to first brood at concentrations ≥10 µg ai/L. The NOAEC = 4.8 µg ai/L. The study is acceptable. This study was conducted because two previously submitted studies did not establish NOAECs (MRID 46950133 and 47648603). Although this study established a NOAEC, it was at a higher concentration than those showing effects in the two previously conducted studies. There are uncertainties about the previously conducted studies (e.g., potential solvent effects and minimal replication; further discussed in DP407755 (2/2012)); however, there is no evidence that the effects in those studies should be discounted and there is not a clear reason why the older studies showed effects at lower test concentrations than observed in the most recent study.

All three studies showed that difenoconazole has effects on the number of offspring. The NOAEC in the current study (4.8 µg ai/L) is consistent with a NOAEC (1.1 µg ai/L) based on an acute-to-chronic ratio using daphnia (acute; MRID 42245110 and chronic; MRID 42245114) and mysid (acute; MRID 42245111) data. One possibility for the different results among the mysid studies is that small differences in study conditions or the test populations elicited slightly different sensitivities to difenoconazole. Given the available information, additional testing is unlikely to add substantial value to the risk assessment (conclusions) and is therefore not requested at this time. However, additional testing could be recommended in the future if it appears that it would impact the risk assessment. For example, mitigation efforts related to

[10] http://infotrek.er.usgs.gov/nawqa_queries/jsp/swmaster.jsp
[11] www.cdpr.ca.gov/docs/emon/ehap.htm

endangered species could be based on overly conservative assumptions without a definitive endpoint. In the meantime, risk can be assessed using the NOAEC (4.8 µg ai/L) from this study as a lower bound estimate of risk and can be further characterized using the results from the older studies (NOAECs < 0.31 and < 0.115 µg ai/L).

Table 6. Summary of Most Sensitive Aquatic Taxa Toxicity Endpoints for Difenoconazole

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} = 810	42245107
Chronic – Freshwater Fish	Fathead minnow (*Pimephales promelas*)	NOAEC = 1.9 LOAEC = 3.7 based on reduced male length of F0-generation 12 weeks post-hatch	48453205
	Rainbow trout (*Oncorhynchus mykiss*)	NOAEC = 0.86 Value used for risk assessment. Based on acute-to-chronic ratio of fathead minnow data to rainbow trout data (the most acutely sensitive species).[1]	-
Acute – Freshwater Invertebrate	Water flea (*Daphnia magna*)	48-hr EC_{50} = 770	42245110
Chronic – Freshwater Invertebrate	Water flea (*Daphnia magna*)	NOAEC = 5.6 LOAEC = 13.0 based on reduced number of young/adult/reproductive day and adult length	42245114
Chronic – Freshwater Invertebrate (Sediment)	Midge (*Chironomus riparius*)	EC_{50} >50 mg ai/kg-sediment (nominal) NOAEC = 5 mg ai/kg-sediment (nominal) LOAEC = 50 mg ai/kg-sediment (nominal) based on emergence rate & development rate	47648601
Acute – Estuarine/Marine Fish	Sheepshead minnow (*Cyprinodon variegates*)	96-hr LC_{50} = 819	42245112
Chronic – Estuarine/Marine Fish	Sheepshead minnow (*Cyprinodon variegates*)	NOAEC = 0.86 Based on acute-to-chronic ratio of fathead minnow data to sheepshead minnow data.[1]	-
Acute – Estuarine/Marine Mollusk	Eastern oyster (*Crassostrea virginica*)	96-hr EC_{50} = 424	42906701
Acute – Estuarine/Marine Invertebrate	Mysid shrimp (*Americamysis bahia*)	96-hr LC_{50} = 150	42245111
Chronic – Estuarine/Marine Invertebrate	Mysid shrimp (*Americamysis bahia*)	NOAEC < 0.115 LOAEC ≤ 0.115 based on reduced number of young/adult/reproductive day NOAEC = 4.8 LOAEC = 10 based on F0 post-pairing survival, offspring/female, time to first brood	46950133 49322901 and 49387801

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Vascular Plant – Freshwater	Duckweed (*Lemna gibba*)	EC_{50} = 1900 EC_{05} = 110 NOAEC < 110 LOAEC ≤ 110 based on reduced frond number	46950204
Non-vascular Plant	Diatom (*Navicula pelliculosa*)	EC_{50} = 98 NOAEC = 53 LOAEC = 150 based on reduced cell density	46950208

[1] Acute toxicity to fathead minnow: LC_{50} = 1800 µg ai/L (MRID 48453201)

Table 7. Summary of Most Sensitive Terrestrial Taxa Toxicity Endpoints for Difenoconazole

Type of Study	Species	Toxicity Value	MRID
Acute – Avian Oral Dose	Canary (*Serinus canaria*)	LD_{50} > 2000 mg ai/kg-bw	48453202
Acute – Avian Dietary	Bobwhite quail (*Colinus virginianus*)	LC_{50} = 4579 mg ai/kg-diet	42245103
Chronic – Avian Dietary	Bobwhite quail (*Colinus virginianus*)	NOAEC = 21.9 mg ai/kg-diet LOAEC = 108 mg ai/kg-diet based on reduction in hatchling body weight	46950202
Acute – Mammalian Oral Dose	Laboratory rat (*Rattus norvegicus*)	LD_{50} = 1453 mg ai/kg-bw	42090006
Two Generation Reproduction – Mammalian	Laboratory rat (*Rattus norvegicus*)	NOAEC = 25 mg ai/kg-diet LOAEC = 250 mg ai/kg-diet	42090018
Acute Contact – Terrestrial Invertebrate	Honey bee (*Apis mellifera*)	LD_{50} >100 µg ai/bee	42245124
Acute Contact – Terrestrial Invertebrate	Earthworm	LC_{50} > 610 mg ai/kg-dw	42245125
Terrestrial Plants	Corn, Onion, Ryegrass, Wheat, Radish, Cabbage, Lettuce, Sugar beet, Soybean, and Tomato	Seedling Emergence EC_{25} > 0.111/0.112 lb ai/A[1] NOAEC < 0.111/0.112 lb ai/A[1,2] Vegetative Vigor EC_{25} > 0.123 lb ai/A NOAEC ≥ 0.123 lb ai/A	48453203 48453204

[1] Some species were exposed to 0.111 lb ai/A and others were exposed to 0.112 lb ai/A.
[2] Effects at 0.11 lb ai/A on lettuce, sugar beet, and soybean were considered biologically significant. Lettuce showed reduced emergence (21%), survival (17%), shoot length (26%), and dry weight (24%). Soybean showed reduced shoot length (23%). Sugar beet showed reduced survival (18%).

1,2,4-triazole (PC 600074)

Available guideline data are presented in **Table 8** and **9**. 1,2,4-triazole is less toxic than difenoconazole to freshwater fish and invertebrates on an acute basis.

The recently submitted avian acute oral toxicity of 1,2,4-triazole study (MRID 49380701) showed increased toxicity (LD_{50} = 770 mg ai/kg bw) compared to difenoconazole (LD_{50} > 2000 mg ai/kg bw for canary; MRID 48453202 and LD_{50} > 2150 mg ai/kg bw for mallard duck; MRID 42245105). This study is acceptable. Reduced body weight and reduced feed consumption were observed at doses ≥ 392 mg ai/kg bw. Clinical signs of toxicity were observed at dose levels ≥ 754 mg ai/kg bw; effects included ruffled appearance, lethargy, wing droop, loss of coordination, lower limb weakness, prostrate posture, loss of righting reflex, depression, shallow and rapid respiration and minor muscle fasciculation.

Non-guideline summary report data on acute oral toxicity to rats (MRID 45284004 and 45284001) suggests that 1,2,4-triazole and difenoconazole are equally as toxic. A 1,2,4-triazole toxicity study with freshwater algae (MRID 45880401) is in review. None of these data are used in the risk assessment.

Ecological Structure Activity Relationship (ECOSAR) methods[12] were used to predict 1,2,4-triazole toxicity to aquatic non-vascular plants and chronic toxicity to fish and invertebrates based on its structural similarity to chemicals for which aquatic toxicity data are known (**Appendix G**). A comparison of 1,2,4-triazole ECOSAR estimates to experimentally derived difenoconazole toxicity endpoints suggests that 1,2,4-triazole is not more toxic than difenoconazole to aquatic non-vascular plants, fish (chronic basis), or aquatic freshwater invertebrates (chronic basis). There is reasonable confidence in the ECOSAR estimates (at least for fish) given that the ECOSAR estimate of acute toxicity to fish is similar to toxicity observed in available studies.

Table 8. Summary of Most Sensitive Aquatic Taxa Toxicity Endpoints for 1,2,4-Triazole

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} = 498,000	48474301
Acute – Freshwater Invertebrate	Water flea (*Daphnia magna*)	48-hr EC_{50} > 98,100	48453206

Table 9. Summary of Most Sensitive Terrestrial Taxa Toxicity Endpoints for 1,2,4-Triazole

Type of Study	Species	Toxicity Value	MRID
Acute – Avian Oral Dose	Bobwhite quail (*Colinus virginianus*)	LD_{50} = 770 mg ai/kg-bw	49380701
Two Generation Reproduction – Mammalian	Laboratory rat (*Rattus norvegicus*)	NOAEC < 250 mg ai/kg-diet LOAEC ≤ 250 mg ai/kg-diet	46467304

<u>Triazole Acetic Acid (PC 600082)</u>

Available data are presented in **Table 10** and **11**. Triazole acetic acid is less toxic than difenoconazole to freshwater fish and invertebrates on an acute basis.

A comparison of triazole acetic acid ECOSAR estimates to experimentally derived difenoconazole toxicity endpoints suggests that triazole acetic acid is not more toxic than difenoconazole to aquatic non-vascular plants, fish (chronic basis), or aquatic freshwater invertebrates (chronic basis) (**Appendix G**). There is no basis for judging confidence in the

[12] ECOSAR predictive software is available publically though the Epi Suite™ program. http://www.epa.gov/oppt/exposure/pubs/episuite.htm

ECOSAR estimates because the ECOSAR estimates for acute toxicity to fish and invertebrates are substantially greater (less toxic) than the non-definitive endpoints observed in the available acute toxicity studies.

Table 10. Summary of Most Sensitive Aquatic Taxa Toxicity Endpoints for Triazole Acetic Acid

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} > 101,000	48453209
Acute – Freshwater Invertebrate	Water flea (*Daphnia magna*)	48-hr EC_{50} > 108,000	48453208

Table 11. Summary of Most Sensitive Terrestrial Taxa Toxicity Endpoints for Triazole Acetic Acid

Type of Study	Species	Toxicity Value	MRID
Acute – Mammalian Oral Dose	Laboratory rat (*Rattus norvegicus*)	LD_{50} > 5000 mg ai/kg-bw	45596802

<u>CGA-205375</u>

On an acute oral basis, CGA-205375 and difenoconazole are of similar toxicity to mammals (**Table 7 and 12**).

A comparison of CGA-205375 ECOSAR estimates to experimentally derived difenoconazole toxicity endpoints suggests that CGA-205375 is not more toxic than difenoconazole to aquatic organisms in general and is similar in toxicity (< 10 times difference) to aquatic non-vascular plants, fish (acute basis), and invertebrates (acute basis) (**Appendix G**). The available information also suggests that CGA-205375 and difenoconazole are similar in chronic toxicity to freshwater fish and invertebrates based on ECOSAR estimates of both compounds (< 10 times difference) and to a lesser extent when based on comparison of CGA-205375 ECOSAR estimates to experimentally derived difenoconazole data. CGA-205375 data are not available to judge the level of confidence in the ECOSAR estimates.

Table 12. Summary of Most Sensitive Terrestrial Taxa Toxicity Endpoints for CGA-205375

Type of Study	Species	Toxicity Value	MRID
Acute – Mammalian Oral Dose	Mouse	LD_{50} = 2309 mg ai/kg-bw[1]	46950303

[1] LD_{50} = 1289 mg ai/kg-bw scaled to laboratory rat weight (350 g) based on an average mouse body weight of 34 g in this study and the following equation: mouse LD_{50} * (mouse bw/rat bw)$^{0.25}$

7.1 Incidents

Reviews were conducted of the Ecological Incident Information System (EIIS, version 2.1.1)[13], the Agency's Aggregated Incidents Reports database, and the Avian Incident Monitoring System

[13] www.epa.gov/espp/consultation/ecorisk-overview.pdf

(AIMS)[14] on November 21, 2014. No incidents were reported in EIIS or AIMS. Ten minor plant damage incidents were reported for one difenoconazole product (Revus Top) in the aggregated incident database. The Revus Top label indicates that it is a dual ai product containing mandipropamid, a fungicide, as well as difenoconazole. No incidents were reported for the assessed products (Inspire, Inspire Super, Inspire XT, Quadris Top, Academy, and Alibi Flora); none of which contain mandipropamid.

8. Ecological Risk Summary

8.1 Potential Risks of Difenoconazole Exposure to Terrestrial Organisms

8.1.1 Birds and Mammals

As in past risk assessments[15] of similar rates there is not an acute risk concern for birds or mammals from the proposed uses. However, there is a chronic risk concern for both listed and non-listed bird and mammal species.

<u>*Surface-residue exposure*</u>

Risk from difenoconazole was not reassessed because the proposed application rates are the same as previously assessed rates. However, degradate risk was considered based on available toxicity data because it was not included in previous assessments:

> Birds are more acutely sensitive to 1,2,4-triazole than to difenoconazole. However, 1,2,4-triazole surface-residue exposure is not an acute risk concern for birds from the proposed uses (RQs < 0.1; listed species LOC = 0.1; representative RQs presented in **Appendix A, Table A-2**). Toxicity data are not available for 1,2,4-triazole (chronic), triazole acetic acid (acute and chronic), and CGA-205375 (acute and chronic).
>
> Compared to difenoconazole, mammals are equally sensitive to CGA-205375 and less sensitive to triazole acetic acid on an acute basis. There is not an acute risk concern for CGA-205375 or triazole acetic acid for mammals from the proposed uses (RQs < 0.1; listed species LOC = 0.1; representative RQs presented in **Appendix A, Table A-3**).[16] Guideline acute toxicity data are not available for 1,2,4-triazole.
>
> Mammalian chronic toxicity data are available for 1,2,4-triazole. It appears that 1,2,4-triazole is at least as toxic as difenoconazole because both compounds showed effects at 250 mg ai/kg-diet; however, there is uncertainty about the relative chronic toxicity of the two compounds because a NOAEC was established in the difenoconazole study (25 mg ai/kg-diet) whereas the 1,2,4-triazole study did not test below 250 mg ai/kg-diet. Although there is uncertainty about the relative chronic toxicity of 1,2,4-triazole and difenoconazole, the risk conclusions are not impacted; that is, there is a chronic risk concern for mammals for all

[14] www.abcbirds.org/abcprograms/policy/toxins/aims/aims/index.cfm

[15] For example, DP333319 and DP340041 (7/2007); DP361251 (8/2009); DP377719 (7/2010)

[16] Conservative surface-residue RQs were based on toxicity to CGA-205375 (slightly greater than that of difenoconazole) and EECs that account for the potential formation of all degradates (the annual application rate was assumed to be applied in a single application).

proposed uses of difenoconazole. Chronic toxicity data are not available for triazole acetic acid or CGA-205375.

Due to a lack of data, this risk assessment may underestimate acute risk to birds and mammals if any degradates are substantially more toxic than difenoconazole.[17] Furthermore, difenoconazole degradates may contribute to the chronic risk concern for birds and mammals to the extent that their toxicity equals or exceeds that of difenoconazole. Submission of additional toxicity data could be useful for better refining the likelihood of risk.

Although treatment is performed indoors, there is a potential chronic risk concern for birds and mammals consuming greenhouse grown vegetables and ornamentals treated with Alibi Flora once the plants are transferred outside given that difenoconazole is persistent and that there is no label restriction on the interval between the last treatment and when plants can be transferred outside. According to the registrant, ornamentals and vegetable transplants treated with Alibi Flora (1) will leave a commercial production site and enter the consumer retail chain and (2) will not be retreated because there are no consumer-formulated products to allow retreatment (email dated 9/5/2013 from Ron Hampton, Syngenta Crop Protection, LLC to Rose Mary Kearns and Tony Kish, Registration Division, EPA). Therefore, it is assumed that risk from outdoor use of Alibi Flora covers risk from indoor use of Alibi Flora.

Contaminated fish exposure

There is not an acute risk concern for piscivorus birds or mammals from the proposed uses (RQs ≤ 0.01; listed species LOC = 0.05; **Table 13**).

There is a chronic risk concern for piscivorus mammals from all of the proposed uses (RQs = 2-7; LOC = 1.0). The LOC is also exceeded for piscivorus birds (RQs = 0.74-1.01; LOC = 1.0), but only larger birds of a single feeding group (birds consuming only fish from the aquatic food web) and only some of the proposed uses. TTR EECs may overestimate bioaccumulation potential because they account for contributions of degradates that have little bioaccumulation potential (i.e., 1,2,4-triazole and triazole acetic acid); however, there is also a chronic risk concern for mammals based on difenoconazole-only EECs. The LOC is exceeded for at least one crop-scenario / application-method combination for all proposed outdoor uses when based on difenoconazole-only EECs. In contrast, the LOC is not exceeded for birds when based on difenoconazole-only EECs but those EECs do not account for the contribution of CGA-205375 which is expected to bioaccumulate like difenoconazole.

Table 13. Piscivorous Wildlife RQs for Proposed Use of Difenoconazole[1,2,3,4]

Crop	Wildlife Species	Acute RQ		Chronic RQ	
		Dose Based	Dietary Based	Dose Based	Dietary Based
Cucurbit; aerial application (highest TTR EECs) and	*Mammalian*				
	fog/water shrew	<0.01	N/A	**2-3**	≤0.58
	rice rat/star-nosed mole	<0.01	N/A	**3-4**	≤0.58
	small mink	<0.01	N/A	**4-5**	≤0.82
	large mink	<0.01	N/A	**4-6**	≤0.82

[17] Non-guideline summary data suggests that 1,2,4-triazole and difenoconazole are equal in acute toxicity to rats.

Crop	Wildlife Species	Acute RQ		Chronic RQ	
		Dose Based	Dietary Based	Dose Based	Dietary Based
Artichoke & Tree Nuts; ground application (lowest TTR EECs)	small river otter	<0.01	N/A	**4-6**	≤0.82
	large river otter	<0.01	N/A	**5-7**	≤0.89
	Avian				
	sandpipers	≤0.014	<0.01	N/A	≤0.67
	cranes	<0.01	<0.01	N/A	≤0.68
	rails	<0.01	<0.01	N/A	≤0.78
	herons	<0.01	<0.01	N/A	≤0.80
	small osprey	<0.01	<0.01	N/A	≤0.93
	white pelican	<0.01	<0.01	N/A	0.74-**1.01**

[1] Range is based on the proposed uses resulting in the lowest and highest TTR EECs (artichoke & tree nuts – ground application and cucurbit – aerial application; **Appendix D, Table D-1**).
[2] Concentration in water is based on an averaging period of 4 days (closest TTR EEC to the 9-day KABAM estimated time to steady state). It was assumed that the pore water TTR EEC = surface water TTR EEC because the GENEEC model does not provide pore water concentrations.
[3] RQs greater than 2 (chronic) are rounded to the nearest whole number.
[4] It is assumed that the toxicity of CGA-205375 is the same as difenoconazole in the absence of data. Acute RQs for mammals are based on difenoconazole toxicity (LD_{50} = 1453 mg ai/kg bw for rat); however, risk conclusions for acute risk to piscivorus mammals would not change if based on CGA-205375 toxicity (LD_{50} = 2309 mg ai/kg bw for mouse).
BOLD indicates that the RQ is greater than or equal to the chronic LOC (1.0).

There is some uncertainty about the chronic risk concern for mammals and birds because the BCF study showed a depuration half-life of one day for all radiolabeled compounds (i.e., difenoconazole, CGA-205375, and any other degradates). Although the study suggests rapid loss of bioaccumulated difenoconazole and CGA-205375 from fish when exposure is removed under laboratory conditions, difenoconazole is persistent in the environment. Thus, under some circumstances there may be reduced risk for piscivorus animals; for example, sustained bioaccumulation may be lower in aquatic food webs only temporarily or sporadically exposed to difenoconazole (e.g. in sections of flowing water bodies with pulses of difenoconazole and CGA-205375). In contrast, bioaccumulation may be greater and more sustained for food webs in static water bodies because it is likely to take longer for difenoconazole to dissipate from these aquatic environments.

The assessment assumed that CGA-205375 toxicity is the same as difenoconazole due to a lack of data (acute for birds and chronic for birds and mammals). Risk conclusions are the same for acute toxicity to mammals based on either difenoconazole or CGA-205375 toxicity. Acute risk to birds may be underestimated only if CGA-205375 is substantially more toxic than difenoconazole. Other the other hand, if CGA-205375 is slightly more toxic to birds on a chronic basis then there would be greater certainty in the potential risk concern; that is, there would be a greater number of size-class / feeding-group combinations and crop-scenario / application-method combinations exceeding the LOC. The chronic risk concern for mammals is not impacted by CGA-205375 toxicity; however, the level of confidence in the concern could change if CGA-205375 toxicity differs substantially from difenoconazole.

8.1.2 Terrestrial Plants

There is not a risk concern for monocots (non-listed or listed species) from the proposed uses. RQs were not calculated because the available toxicity studies resulted in non-definitive EC_{25}s and NOAECs (no effects were observed). However, a conservative comparison can be made between EECs and the highest concentration tested in the toxicity studies. EECs for plants located in dry or semi-aquatic locations and for plants exposed to spray drift are less than the highest test concentration (**Appendix C, Table C-3**).[18]

Risk to dicots is less clear because there is uncertainty regarding the toxicity to dicots even though statistical significance was not detected in the seedling emergence study. The lack of statistical significance for three of the dicots (lettuce, soybean, and sugar beet) may have been due to the high experimental variability and the magnitude of some of the effects is considered potentially biologically significant. Lettuce showed reduced emergence (21%), survival (17%), shoot length (26%), and dry weight (24%). Soybean showed reduced shoot length (23%). Sugar beet showed reduced survival (18%).

There is not a risk concern for non-listed dicots from the proposed uses assuming that the $EC_{25} \approx$ 0.111/0.112 lb ai/A (the test concentration[19]) in the seedling emergence study; this may be a reasonable assumption given that the maximum observed effect was 26%. RQs were not calculated; however, a conservative comparison can be made between EECs and the visually estimated EC_{25}. EECs for plants located in dry or semi-aquatic locations and for plants exposed to spray drift are less than the highest test concentration (**Appendix C, Table C-3**).

Risk to listed dicot species cannot be precluded given the presumed biological significance and magnitude of the observed inhibition at 0.111 lb ai/A for lettuce, soybean, and sugar beet. Depending on the proposed use, the NOAEC would need to be only about three to four times lower than 0.111 lb ai/A to have a risk concern for semi-aquatic listed dicots. Tier II testing of lettuce, soybean, and sugar beet would reduce uncertainty of the risk to listed dicot species. One dual ai (difenoconazole and mandipropamid) product, Revus Top, was associated with ten minor plant damage incidents; however, it is uncertain if one compound caused the damage and if so which one or if there was a synergistic effect from the two compounds. No incidents were reported for the currently assessed products.

8.1.3 Terrestrial Invertebrates

There is not an acute contact risk concern for bees from the proposed uses. Acute contact-based RQs were not calculated because the available toxicity study resulted in a non-definitive endpoint. However, a conservative comparison can be made between EECs and the highest concentration tested in the toxicity study. The EEC (0.351 µg ai/bee) for the highest proposed single application rate is less than 1/2.5 of the non-definitive LD_{50} (>100 µg ai/bee)[20]. There is uncertainty about risk from dietary exposure due to a lack of toxicity studies.

Risk to earthworms appears to be low for the proposed uses. A previous assessment presented an EEC in soil of 0.28 mg/kg-dry soil (see DP333319 and DP340041, 7/12/2007) for use on

[18] LOC = 1.0 for listed and non-listed plants
[19] Some species were exposed to 0.111 lb ai/A and others were exposed to 0.112 lb ai/A.
[20] LOC = 0.4

ornamentals (0.56 lb ai/A/season[21]) which is over three orders of magnitude below the non-definitive 14-day NOAEC for earthworm (no effects were observed at the highest test concentration; 610 mg ai/kg-dw). As in past assessments, there is not a risk concern for earthworms from the proposed uses given that the proposed application rates are lower than the previously considered rate.

8.2 Potential Risks of Difenoconazole Exposure to Aquatic Organisms

8.2.1 Fish

There is not an acute risk concern for fish from the proposed uses. The acute listed-species LOC (0.05) is not exceeded for freshwater or estuarine/marine fish (RQs ≤ 0.02; **Table 14**).

There is a chronic risk concern for fish (listed and non-listed species) from all of the proposed uses. The chronic LOC (1.0) is exceeded for freshwater and estuarine/marine fish (RQs = 12.0-16.6) based on TTR EECs (**Table 15**). Despite uncertainty about degradate toxicity, it is important to note that the chronic LOC is exceeded based on difenoconazole-only EECs as well.

Table 14. Acute Risk Quotients for Freshwater and Estuarine/Marine Fish Exposed from the Proposed Difenoconazole Uses (TTR EEC)

Peak EEC (μg/L)[1]	Freshwater Acute RQ (LC_{50} = 810 μg/L)	Estuarine/Marine Acute RQ (LC_{50} = 819 μg/L)
11.2-15.4	0.01-0.02	0.01-0.02

[1] Range represents scenarios resulting in the lowest and highest TTR EECs (artichoke & tree nuts - ground application and cucurbit – aerial application, **Appendix D, Table D-1**).

Table 15. Chronic Risk Quotients for Freshwater and Estuarine/Marine Fish Exposed from the Proposed Difenoconazole Uses (TTR EEC)

60-day EEC (μg/L)[1]	Freshwater and Estuarine/Marine Chronic RQ (NOAEC = 0.86 μg/L)
10.31-14.24	**12.0-16.6**

[1] Range represents scenarios resulting in the lowest and highest TTR EECs (artichoke & tree nuts - ground application and cucurbit – aerial application, **Appendix D, Table D-1**).
BOLD exceeds chronic LOC (1.0).

8.2.2 Aquatic Invertebrates

There is not an acute risk concern for aquatic freshwater invertebrates from the proposed uses (RQs ≤ 0.02, **Table 16**). There is an acute risk concern for aquatic marine/estuarine invertebrates (only listed species) from all of the proposed uses. The acute listed-species LOC (0.05) is exceeded for estuarine/marine aquatic invertebrates (RQs = 0.07-0.10) for all of the proposed outdoor uses. As previously discussed, risk to marine/estuarine invertebrates may be overestimated when based on TTR EECs because toxicity data indicate that in comparison to

[21] Although the modeled rate was 0.56 lb ai/A/season, it appears that this was in error. Previous, current, and proposed labels (Inspire and Alibi Flora) state a seasonal, crop, or annual maximum of 0.52 lb ai/A for ornamental use.

difenoconazole, freshwater invertebrates are less sensitive to two of the degradates included in the TTR EECs (1,2,4-triazole and triazole acetic acid). However, there is still an acute risk concern based on difenoconazole-only EECs; the acute listed-species LOC is exceeded for estuarine/marine invertebrates (RQs = 0.012-0.075) for all the proposed outdoor uses except artichoke, ginseng, and tree nuts[22].

Table 16. Acute Risk Quotients for Freshwater and Estuarine/Marine Invertebrates Exposed from the Proposed Difenoconazole Uses (TTR EEC)

Peak EEC (µg/L)[1]	Freshwater Acute RQ (LC_{50} = 770 µg/L)	Estuarine/ Marine Acute RQ (LC_{50} = 150 µg/L)
11.2-15.4	0.01-0.02	**0.07-0.10**

[1] Range represents scenarios resulting in the lowest and highest TTR EECs (artichoke & tree nuts - ground application and cucurbit – aerial application, **Appendix D, Table D-1**).
BOLD exceeds acute listed-species LOC (0.05).

There is a chronic risk concern for aquatic invertebrates (listed and non-listed species) from all of the proposed uses.

The chronic LOC (1.0) is exceeded for water-column freshwater invertebrates (RQs = 1.94-2.68) based on TTR EECs (**Table 17**). If the three degradates (1,2,4-triazole, triazole acetic acid, and CGA-205375) are less toxic than difenoconazole on a chronic basis then there would not be a chronic risk concern for freshwater invertebrates from the proposed artichoke use (RQ ≤ 0.89 based on 21-day difenoconazole-only EEC = 5 µg/L for aerial applications) and some crop-scenario / application-method combinations for other proposed uses (i.e., those with 21-day difenoconazole-only EECs < 5.6 µg/L, see **Appendix D**, **Table D-1**). Therefore, guideline chronic toxicity data with the major degradates (1,2,4-triazole, triazole acetic acid, and CGA-205375) would be useful for refining the risk conclusions for some difenoconazole uses if they demonstrate less toxicity than difenoconazole.

Table 17. Chronic Risk Quotients for Freshwater and Estuarine/Marine Invertebrates Exposed from the Proposed Difenoconazole Uses (TTR EEC)

21-day EEC (µg/L)[1]	Freshwater Chronic RQ (NOAEC = 5.6 µg/L)	Estuarine/Marine Chronic RQ (NOAEC = 4.8 µg/L)[2]
10.86-14.99	**1.94-2.68**	**2.26-3.12**[3]

[1] Range represents scenarios resulting in the lowest and highest TTR EECs (artichoke & tree nuts - ground application and cucurbit – aerial application, **Appendix D, Table D-1**).
[2] This NOAEC is an upper bound estimate on toxicity. Two additional toxicity studies showed NOAECs < 0.31 and <0.115 µg/L
[3] Lower bound estimate of risk. RQs > 94 based on NOAEC < 0.115 µg/L and EEC = 10.86 µg/L.
BOLD exceeds chronic LOC (1.0).

The chronic LOC (1.0) is exceeded for water-column estuarine/marine invertebrates based on TTR EECs (RQs = 2.26 to > 94 depending on the use and toxicity data, **Table 17**). While there

[22] At least one crop-scenario / application-method combination exceeds the listed-species LOC for all proposed outdoor uses except artichoke, ginseng, and tree nuts.

is not uncertainty about the risk concern for the proposed uses, there is uncertainty about the magnitude of the RQs. As discussed earlier, there is uncertainty about the highest difenoconazole concentration that does not elicit chronic effects in mysid. The definitive endpoint established in the most recent study (MRID 49322901 and 49387801; NOAEC = 4.8 µg ai/L) can be considered a lower bound estimate of risk (RQs = 2.26-3.12). Results from the two older studies (MRID 46950133 and 47648603, NOAEC < 0.31 µg ai/L and < 0.115 µg ai/L) cannot be discounted and suggest that the likelihood of potential effects resulting from the proposed uses is even greater that the lower bound estimate of risk. Likewise, RQs are about four times higher than the lower bound estimate of risk when based on an ACR-derived NOAEC estimate for mysid (1.1 µg ai/L). There is also uncertainty about the toxicity of the major degradates (1,2,4-triazole, triazole acetic acid, and CGA-205375); however, if the three degradates are less toxic than difenoconazole on a chronic basis then there would still be a chronic risk concern for estuarine/marine invertebrates from the proposed uses. Although a few crop-scenario / application-method combinations would exceed the LOC based on the lower bound estimate of risk (21-day difenoconazole-only EECs < 4.8 µg ai/L, see **Appendix D**, **Table D-1**), at least one crop scenario exceeds the LOC for each proposed use and all modeled EECs exceed the LOC based on the ACR-derived NOAEC and non-definitive NOAECs from available studies.

Risk to benthic invertebrates was considered given the fate properties of difenoconazole. Risk was not assessed using the submitted chronic toxicity range-finding study (MRID 47648601) due to problems with the study design. Instead, risk to benthic invertebrates was considered using water column invertebrate data (*Daphnia* and *Americamysis*) as surrogates. Pore water difenoconazole concentrations were determined using SWCC[23] (**Appendix D, Table D-2**) and are similar to water column concentrations (**Table D-1**). The risk concern for water column species is protective of benthic species in general (i.e., there is a risk concern); however, risk may be over or underestimated and the magnitude of the RQ associated with that concern is uncertain without toxicity data for benthic invertebrates.

8.2.3 Aquatic Plants

There is not a risk concern for aquatic plants from the proposed uses based on available information. There is not a LOC exceedance for listed or non-listed species (**Table 18**). There is some uncertainty about risk to non-vascular aquatic plants because an acceptable study with blue green algae (cyanobacteria) is not available. There are not currently any listed non-vascular plants so the uncertainty is for non-listed species. Blue-green algae would need to be about 6-9 times more sensitive than *Navicula pelliculosa* to exceed the LOC (non-listed species) for the proposed uses assuming that the degradates (1,2,4-triazole, triazole acetic acid, and CGA-205375) and difenoconazole are equal in toxicity.

[23] GENNEC does not provide pore water concentrations; therefore, difenoconazole-only EECs were used instead of TTR EECs for considering risk to benthic invertebrates.

Table 18. Risk Quotients for Aquatic Plants Exposed to Difenoconazole from the Proposed Difenoconazole Uses (TTR EEC)

Peak EEC (μg/L)[1]	Vascular Plant Non-listed RQ (EC_{50} = 1900 μg/L)	Vascular Plant Listed RQ (EC_{05} = 110 μg/L)	Non-vascular Plant Non-listed RQ (EC_{50} = 98 μg/L)	Non-vascular Plant Listed RQ (NOAEC = 53 μg/L)
15.4	0.01	0.14	0.16	0.29

[1] Scenario resulting in the highest TTR EECs (cucurbit – aerial application, **Appendix D**, **Table D-1**).

8.3 Risk Summary

The primary risk concerns from the proposed outdoors uses are for chronically exposed listed and non-listed aquatic invertebrate (estuarine/marine), fish, bird, and mammal species. In addition, there is an acute risk concern for listed aquatic invertebrate (marine/estuarine) species and a risk concern cannot be precluded for terrestrial dicots (listed species) based on the available data.

References

USEPA, 2014. Guidance for Assessing Pesticide Risks to Bees. Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention.

USEPA, 2013. Guidance on modeling off-site deposition of pesticides via spray drift for ecological and drinking water assessments. Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention.

USEPA, 2009. Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides (Version 2.1; Oct. 22, 2009). Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention.

Appendix A: Representative T-REX Output

Table A-1. Representative T-REX Surface-Residue EECs for Difenoconazole (Field Use on Cucurbit Vegetables, Inspire Super label)

Size Class (grams)	Dietary and Dose-Based EECs[1]				
	Short Grass	Tall Grass	Broadleaf Plants	Fruits/Pods/ Seeds	Arthropods
Mammals					
Dose-Based EECs					
15	82.45	37.79	46.38	5.15	32.29
35	56.98	26.12	32.05	3.56	22.32
1000	13.21	6.05	7.43	0.82	5.17
Dietary-Based EECs[2]					
NA	86.48	39.63	48.64	5.40	33.87
Avian					
Dose-Based EECs					
20	98.49	45.14	55.40	6.15	38.57
100	56.16	25.74	31.59	3.51	21.99
1000	25.14	11.52	14.14	1.57	9.84
Dietary-Based EECs[2]					
NA	86.48	39.63	48.64	5.40	33.87

[1] 0.06375 lb ai/A (1 application) + 0.114 lb ai/A (4 applications). The 0.06375 lb ai/A application was applied day 0 followed by 0.114 ai/A applications on day 7, 21, 28, and 42. Only 2 sequential applications of difenoconazole are permitted before rotating to another fungicide; therefore a 14 day interval was assumed between the 2nd and 3rd applications and the 4th and 5th applications. EECs are based on default half-life of 35 days.

[2] Size class not used for dietary EECs

* EECs are similar to previously assessed uses.

Table A-2. Representative T-REX Output for 1,2,4-Triazole Exposure to Birds (Ornamental Use)

Acute Avian Dose-Based Risk Quotients[1]													
Size Class (grams)	Adjusted LD50	EECs and RQs											
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/ Seeds		Arthropods		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
20	555	18.64	0.03	8.55	0.02	10.49	0.02	1.17	<0.01	7.30	0.01	0.26	<0.01
100	706	10.63	0.02	4.87	0.01	5.98	0.01	0.66	<0.01	4.16	0.01	0.15	<0.01
1000	998	4.76	<0.01	2.18	<0.01	2.68	<0.01	0.30	<0.01	1.86	<0.01	0.07	<0.01

[1] Based on 1,2,4-triazole toxicity (LD_{50} = 770 mg ai/kg bw, MRID 49380701) and ornamental use (0.13 lb ai/A*4 applications at 7 days and 14 days between 2nd/3rd application) adjusted to 100% formation of 1,2,4-triazole and the MW ratio of 1,2,4-triazole to difenoconazole (69.07/406.26). Adjusted application rate = 0.022 lb 1,2,4-triazole/A * 4 applications. The maximum formation of 1,2,4-triazole was 20.6% by aerobic soil metabolism and 35.9% by anaerobic aquatic metabolism. Screening-level EECs were based on 100% formation of 1,2,4-triazole because residue formation on plants and insects may be higher or lower than observed in the available fate studies.

Table A-3. Representative T-REX Output for Combined Difenoconazole and Degradate Exposure to Mammals (Ornamental Use)

Acute Mammalian Dose-Based Risk Quotients[1]														
Size Class (grams)	Adjusted LD50	EECs and RQs												
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/ Seeds		Arthropods		Granivore		
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	
15	2833	118.99	0.04	54.54	0.02	66.93	0.02	7.44	<0.01	46.60	0.02	1.65	<0.01	
35	2292	82.24	0.04	37.69	0.02	46.26	0.02	5.14	<0.01	32.21	0.01	1.14	<0.01	
1000	992	19.07	0.02	8.74	0.01	10.73	0.01	1.19	<0.01	7.47	0.01	0.26	<0.01	

[1] RQs were based on CGA-250375 toxicity (LD_{50} = 2309 mg ai/kg bw for 34 gram average bw mice; MRID 46950303) and ornamental use (0.13 lb ai/A*4 applications) applied as a single application of 0.52 lb ai/A. These screening-level surface-residue EECs account for potential exposure to difenoconazole and degradates.

Appendix B: Representative KABAM Input and EECs (Cucurbit Use)

Table B-1. Chemical characteristics of Difenoconazole.

Characteristic	Value
Pesticide Name	Difenoconazole
Log K_{OW}	4.4
K_{OW}	25119
K_{OC} (L/kg OC)	5381
Time to steady state (T_S; days)	9
Pore water EEC (µg/L)	15.34 (4 day surface water TTR EEC)
Water Column EEC (µg/L)	15.34 (4 day surface water TTR EEC)

Table B-2. Mammalian and avian toxicity data for Difenoconazole.

Animal	Measure of effect (units)	Value	Species
Avian	LD_{50} (mg/kg-bw)	2150	mallard duck
	LC_{50} (mg/kg-diet)	4579	Northern bobwhite quail
	NOAEC (mg/kg-diet)	21.9	Northern bobwhite quail
	Mineau Scaling Factor	1.15	Default value for all species is 1.15 (for chemical specific values, see Mineau et al. 1996).
Mammalian	LD_{50} (mg/kg-bw)	1453	laboratory rat
	LC_{50} (mg/kg-diet)	N/A	other
	Chronic Endpoint	25	laboratory rat
	units of chronic endpoint*	ppm	

Table B-3. Calculation of EECs for mammals and birds consuming fish contaminated by Difenoconazole.

Wildlife Species	Biological Parameters				EECs (pesticide intake)	
	Body Weight (kg)	Dry Food Ingestion Rate (kg-dry food/kg-bw/day)	Wet Food Ingestion Rate (kg-wet food/kg-bw/day)	Drinking Water Intake (L/d)	Dose Based (mg/kg-bw/d)	Dietary Based (ppm)
Mammalian						
fog/water shrew	0.02	0.140	0.585	0.003	8.573	14.65
rice rat/star-nosed mole	0.1	0.107	0.484	0.011	7.065	14.60
small mink	0.5	0.079	0.293	0.048	6.000	20.45
large mink	1.8	0.062	0.229	0.168	4.688	20.45
small river otter	5.0	0.052	0.191	0.421	3.909	20.45
large river otter	15.0	0.042	0.157	1.133	3.491	22.21
Avian						
sandpipers	0.0	0.228	1.034	0.004	15.1466	14.65
cranes	6.7	0.030	0.136	0.211	2.0341	14.96
rails	0.1	0.147	0.577	0.010	9.8652	17.08
herons	2.9	0.040	0.157	0.120	2.7628	17.55
small osprey	1.3	0.054	0.199	0.069	4.0791	20.45
white pelican	7.5	0.029	0.107	0.228	2.3701	22.21

Appendix C: Representative TerrPlant Output

Table C-1. Chemical Identity

Chemical Name	Difenoconazole
Use	Ornamental
Application Method	Aerial
Solubility in Water (ppm)	15

Table C-2. Input parameters used to derive EECs

Input Parameter	Symbol	Value	Units
Application Rate	A	0.13	
Incorporation	I	1	none
Runoff Fraction	R	0.02	none
Drift Fraction	D	0.05	none

Table C-3. EECs for Difenoconazole (lb ai/A)

Description	Equation	EEC
Runoff to dry areas	(A/I)*R	0.0026
Runoff to semi-aquatic areas	(A/I)*R*10	0.026
Spray drift	A*D	0.0065
Total for dry areas	((A/I)*R)+(A*D)	0.0091
Total for semi-aquatic areas	((A/I)*R*10)+(A*D)	0.0325

Table C-4. Plant survival and growth data used for RQ derivation (lb ai/A)

Plant type	Seedling Emergence		Vegetative Vigor	
	EC_{25}	NOAEC	EC_{25}	NOAEC
Monocot	>0.111	≥0.111	>0.123	≥0.123
Dicot	0.111 (assumed)	ND (effects observed at tested concentration)	>0.123	≥0.123

ND = Not determined

Table C-5. RQ values for plants in dry and semi-aquatic areas exposed to difenoconazole through runoff and/or spray drift.[1]

Plant Type	Listed Status	Dry	Semi-Aquatic	Spray Drift
Monocot	non-listed	<0.1[2]	0.29[2]	<0.1[2]
Monocot	listed	<0.1[2]	0.29[2]	<0.1[2]
Dicot	non-listed	<0.1[3]	0.29[3]	<0.1[3]
Dicot	listed	ND	ND	ND

[1]If RQ > 1.0, the LOC is exceeded, resulting in potential for risk to that plant group.

[2] RQs are overestimates and should not be used because no effects were observed in the toxicity study at the tested concentration.

[3] RQ estimated based on visual assumption that $EC_{25} \approx 0.111$ lb ai/A based on observed effects.

ND = Not determined

Appendix D: SWCC and GENEEC EECs

Table D-1. Surface Water EECs

Water Source (model)	Use (rate and interval)	Crop Scenario	Application Method	Peak EEC (µg/L)	21-Day EEC (µg/L)	60-Day EEC (µg/L)
	Concentrations (EECs) of Difenoconazole only					
Surface Water (SWCC)	Artichoke (4 applications @ 0.115 lb ai/A)	CARowcropSTD	Aerial	5.49	5.00	4.86
	Ginseng (4 applications @ 0.115 lb ai/A)	MNSugarbeetSTD	Aerial	6.55	6.06	5.90
	Bushberry (4 applications @ 0.115 lb ai/A)	NYgrapeSTD	Aerial	11.30	10.10	9.82
			Ground[1]	9.06	8.13	7.90
		ORberriesOP	Aerial	7.10	6.61	6.48
	Legume (4 applications @ 0.115 lb ai/A)	MIbeanSTD	Aerial	8.16	7.47	7.32
		WAbeanNMC	Aerial	5.46	4.96	4.81
	Cucurbit (4 applications @ 0.114 lb ai/A) + 1 application @ 0.064 lb ai/A	CAmelonRLF	Aerial	4.95	4.37	4.22
		FLCucumberSTD	Aerial	8.45	7.18	6.91
	Fruiting vegetable (4 applications @ 0.115 lb ai/A)	FLpepperSTD	Aerial	7.49	6.31	6.08
		PAtomato	Aerial	9.80	8.50	8.17
	Bulb vegetable (4 applications @ 0.115 lb ai/A)	GAonionSTD	Aerial	8.26	7.02	6.62
		CAonionSTD	Aerial	3.47	2.90	2.71
			Ground[1]	1.87	1.59	1.50
	Brassica (cole) leafy vegetables (4 applications @ 0.115 lb ai/A)	CAlettuceSTD	Aerial	8.25	7.62	7.42
		FLcabbageSTD	Aerial	7.24	5.97	5.59
	Tree nuts (4 applications @ 0.115 lb ai/A)	CAalmondsSTD	Aerial	4.66	4.18	4.05
		GApecansSTD	Aerial	6.72	5.68	5.35
		ORfilbertsSTD	Aerial	6.39	5.91	5.76

Water Source (model)	Use (rate and interval)	Crop Scenario	Application Method	Peak EEC (µg/L)	21-Day EEC (µg/L)	60-Day EEC (µg/L)
	Concentrations (EECs) of Difenoconazole only					
	Stone Fruits (4 applications @ 0.115 lb ai/A)	GApeachesSTD	Aerial	5.84	4.29	3.90
		MIcherriesSTD	Aerial	10.90	9.70	9.37
	Ornamentals (4 applications @ 0.13 lb ai/A)	CAnurserySTD	Aerial	5.37	4.78	4.42
		FLNurserySTD	Aerial	6.34	5.42	4.85
		MInurserySTD	Aerial	8.92	8.32	7.99
		ORnurserySTD	Aerial	6.43	5.81	5.47
		TNnurserySTD	Aerial	7.70	6.90	6.56
Surface Water (GENEEC)	*Concentrations (EECs) of Total Toxic Residues (Difenoconazole and Its Degradates)*					
	Cucurbit (5 applications @ 0.114 lb ai/A)[2]	NA	Aerial	15.40	14.99	14.24
	Cucurbit (5 applications @ @ 0.104 lb ai/A)[3]	NA	Aerial	13.98	13.56	12.88
	Artichoke (4 applications @ 0.115 lb ai/A)	NA	Ground	11.17	10.86	10.31

[1] Ground application was modeled for the highest and lowest exposures (i.e. aerial application for NYgrapeSTD and CAonionSTD scenarios) to compare EECs for application methods
[2] GENEEC has a limitation for unequal application rate. Therefore, five applications of maximum application rate of 0.114 lb ai/A were used which is slightly higher (0.57 ai lb/A) than annual maximum rate of 0.52 lb ai/A.
[3] Annual maximum rate of 0.52 lb ai/A (i.e. 0.104 lb ai/A X 5 applications) were used in the modeling, which may underestimate peak value for reduced maximum single rate

Table D-2. Pore Water EECs

Water Source (model)	Use (rate and interval)	Crop Scenario	Application Method	Peak EEC (µg/L)	21-Day EEC (µg/L)
Concentrations (EECs) of Difenoconazole only					
Surface Water (SWCC)	Artichoke (4 applications @ 0.115 lb ai/A)	CARowcropSTD	Aerial	4.64	4.64
	Ginseng (4 applications @ 0.115 lb ai/A)	MNSugarbeetSTD	Aerial	5.65	5.65

Water Source (model)	Use (rate and interval)	Crop Scenario	Application Method	Peak EEC (µg/L)	21-Day EEC (µg/L)
Concentrations (EECs) of Difenoconazole only					
	Bushberry (4 applications @ 0.115 lb ai/A)	NYgrapeSTD	Aerial	9.49	9.49
			Ground[1]	7.66	7.66
		ORberriesOP	Aerial	6.31	6.31
	Legume (4 applications @ 0.115 lb ai/A)	MIbeanSTD	Aerial	7.07	7.06
		WAbeanNMC	Aerial	4.58	4.58
	Cucurbit (4 applications @ 0.114 lb ai/A) + 1 application @ 0.64 lb ai/A	CAmelonRLF	Aerial	3.90	3.90
		FLCucumberSTD	Aerial	6.46	6.46
	Fruiting vegetable (4 applications @ 0.115 lb ai/A)	FLpepperSTD	Aerial	5.65	5.65
		PAtomato	Aerial	7.86	7.86
	Bulb vegetable (4 applications @ 0.115 lb ai/A)	GAonionSTD	Aerial	6.28	6.27
		CAonionSTD	Aerial	2.48	2.48
			Ground[1]	1.38	1.38
	Brassica (Cole) Leafy vegetables (4 applications @ 0.115 lb ai/A)	CAlettuceSTD	Aerial	7.15	7.15
		FLcabbageSTD	Aerial	5.24	5.23
	Tree nuts (4 applications @ 0.115 lb ai/A)	CAalmondsSTD	Aerial	3.83	3.82
		GApecansSTD	Aerial	5.04	5.03
		ORfilbertsSTD	Aerial	5.59	5.59
	Stone Fruits (4 applications @ 0.115 lb ai/A)	GApeachesSTD	Aerial	3.58	3.58
		MIcherriesSTD	Aerial	9.17	9.16
	Ornamentals (4 applications @ 0.13 lb ai/A)	CAnurserySTD	Aerial	4.11	4.10
		FLNurserySTD	Aerial	4.45	4.44
		MInurserySTD	Aerial	7.66	7.65
		ORnurserySTD	Aerial	5.13	5.13

Water Source (model)	Use (rate and interval)	Crop Scenario	Application Method	Peak EEC (µg/L)	21-Day EEC (µg/L)
Concentrations (EECs) of Difenoconazole only					
		TNnurserySTD	Aerial	6.06	6.05
Concentrations (EECs) of Total Toxic Residues (Difenoconazole and Its Degradates)					
Surface Water (GENEEC)	Not applicable for benthic layer				
[1] Ground application was modeled for the highest and lowest exposure (i.e. aerial application for NYgrape and CAmelon scenarios) to compare EECs for application methods					

Appendix E: Example Output of Surface Water Concentrations Calculator (SWCC) Model

Estimated Environmental Concentrations for difenoconazole are presented in Table E-1 for the USEPA standard pond with the NYGrapesSTD field scenario. A graphical presentation of the year-to-year peaks is presented in Figure E-1. These values were generated with the Surface Water Concentration Calculator (SWCC Version 1.106). Critical input values for the model are summarized in Tables E-2 and E-3.

This model estimates that about 3% of difenoconazole applied to the field eventually reaches the water body. The main mechanism of transport from the field to the water body is by erosion (50.3% of the total transport), followed by spray drift (41%) and runoff (8.71%).
In the water body, pesticide dissipates with an effective water column half-life of 1387.8 days. (This value does not include dissipation by transport to the benthic region; it includes only processes that result in removal of pesticide from the complete system.) The main source of dissipation in the water column is metabolism (effective average half-life = 1387.9 days) followed by volatilization (2.8944E+07 days).

In the benthic region, pesticide dissipation is negligible (2770.8 days). The main source of dissipation in the benthic region is metabolism (effective average half-life = 2770.8 days). The vast majority of the pesticide in the benthic region (99.83%) is sorbed to sediment rather than in the pore water.

Table E-1. Estimated Environmental Concentrations (ppb) for Difenoconazole.

Peak (1-in-10 yr)	11.3
4-day Avg (1-in-10 yr)	10.9
21-day Avg (1-in-10 yr)	10.1
60-day Avg (1-in-10 yr)	9.82
365-day Avg (1-in-10 yr)	9.37
Entire Simulation Mean	6.28

Table E-2. Summary of Model Inputs for Difenoconazole.

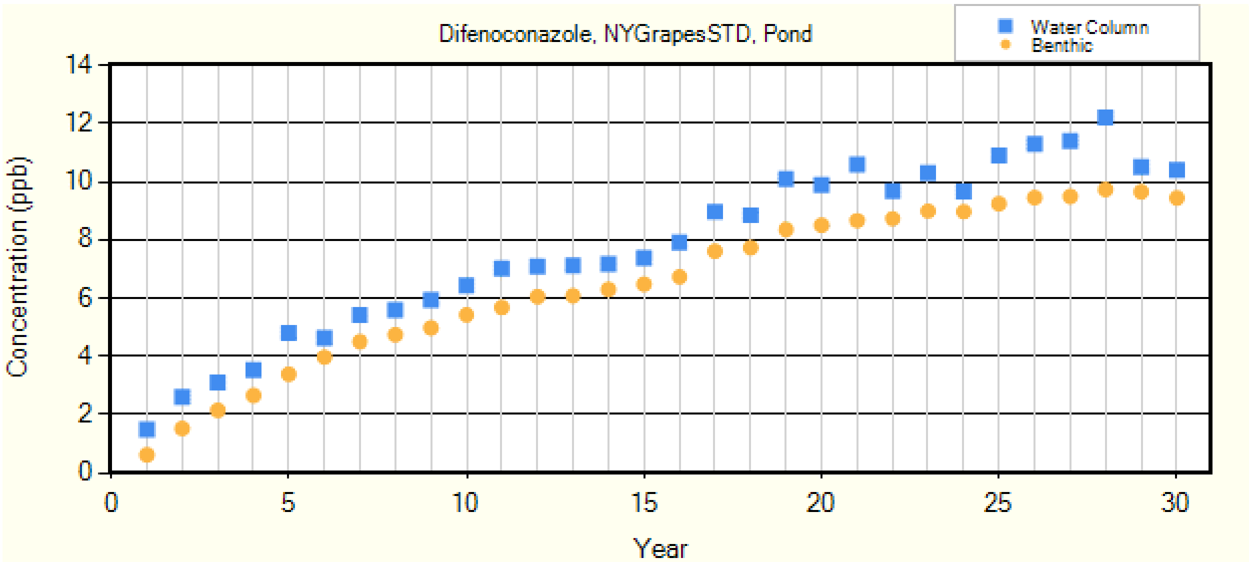
Scenario	NYGrapesSTD
Cropped Area Fraction	1
Koc (ml/g)	5381
Water Half-Life (days) @ 25 °C	556
Benthic Half-Life (days) @ 25 °C	1110
Photolysis Half-Life (days) @ 40 °C	0
Hydrolysis Half-Life (days)	0

Soil Half-Life (days) @ 25 °C	313
Foliar Half-Life (days)	
Molecular Wt	406.27
Vapor Pressure (torr)	2.5E-10
Solubility (mg/l)	15

Table E-3. Application Schedule for Difenoconazole.

Date (Mon/Day)	Type	Amount (kg/ha)	Eff.	Drift
09/10	Foliar	0.129	0.95	0.125
09/17	Foliar	0.129	0.95	0.125
10/01	Foliar	0.129	0.95	0.125
10/08	Foliar	0.129	0.95	0.125

Figure E-1. Yearly Peak Concentrations



Appendix F: Example Output of GENEEC

```
RUN No.   1 FOR Difeniconazole   ON   cucurbit      * INPUT VALUES *
--------------------------------------------------------------------
 RATE (#/AC)   No.APPS &   SOIL  SOLUBIL   APPL TYPE NO-SPRAY INCORP
  ONE(MULT)    INTERVAL    Koc   (PPM )    (%DRIFT)   (FT)     (IN)
--------------------------------------------------------------------
.115(   .575)   5   7    1000.0   15.0   AERL_B( 13.0)     .0    .0


FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)
--------------------------------------------------------------------
METABOLIC  DAYS UNTIL  HYDROLYSIS   PHOTOLYSIS   METABOLIC  COMBINED
 (FIELD)   RAIN/RUNOFF   (POND)     (POND-EFF)    (POND)     (POND)
--------------------------------------------------------------------
    .00        2           N/A       .00-     .00      .00       .00


GENERIC EECs (IN MICROGRAMS/LITER (PPB))     Version 2.0 Aug 1, 2001
--------------------------------------------------------------------
    PEAK      MAX 4 DAY     MAX 21 DAY    MAX 60 DAY    MAX 90 DAY
    GEEC      AVG GEEC       AVG GEEC      AVG GEEC      AVG GEEC
--------------------------------------------------------------------
    15.40       15.34         14.99         14.24         13.71

---------------------------------------------------------------------------

RUN No.   2 FOR Difenoconazole   ON   Cucurbit      * INPUT VALUES *
--------------------------------------------------------------------
 RATE (#/AC)   No.APPS &   SOIL  SOLUBIL   APPL TYPE NO-SPRAY INCORP
  ONE(MULT)    INTERVAL    Koc   (PPM )    (%DRIFT)   (FT)     (IN)
--------------------------------------------------------------------
.104(   .520)   5   7    1000.0   15.0   AERL_B( 13.0)     .0    .0


FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)
--------------------------------------------------------------------
METABOLIC  DAYS UNTIL  HYDROLYSIS   PHOTOLYSIS   METABOLIC  COMBINED
 (FIELD)   RAIN/RUNOFF   (POND)     (POND-EFF)    (POND)     (POND)
--------------------------------------------------------------------
    .00        2           N/A       .00-     .00      .00       .00


GENERIC EECs (IN MICROGRAMS/LITER (PPB))     Version 2.0 Aug 1, 2001
--------------------------------------------------------------------
    PEAK      MAX 4 DAY     MAX 21 DAY    MAX 60 DAY    MAX 90 DAY
    GEEC      AVG GEEC       AVG GEEC      AVG GEEC      AVG GEEC
--------------------------------------------------------------------
    13.93       13.87         13.56         12.88         12.40
```

Appendix G: ECOSAR Results

Table G-1. Comparative Aquatic Toxicity of Difenoconazole and Major Degradation Products

Compound	FW fish 96-hr acute LC_{50} (mg/L)	FW fish chronic NOAEC (mg/L)[1]	FW invertebrate 48-hr acute EC_{50} (mg/L)	FW invertebrate chronic NOAEC (mg/L)[1]	ME fish 96-hr acute LC_{50} (mg/L)	ME fish chronic NOAEC (mg/L)[1]	ME invertebrate 96-hr acute LC_{50} (mg/L)	ME invertebrate chronic NOAEC (mg/L)[1]	Non-vascular plant 96-hr EC_{50} (mg/L)
Difenoconazole	**0.87** (0.81)	**0.007** (0.0009)	**0.95** (0.77)	**0.030** (0.006)	(0.82)	(0.0009)	(0.15)	(<0.000115)	**0.51** (0.30)[2]
1,2,4-triazole	**722.0** (498.0)	**2.2**	**3166.2** (>98.0)	**29.2**	-	-	-		**35.7**
Triazole acetic acid	**51322.1** (>101.0)	**132.3**	**281000.0** (>108.0)	**2132.3**	-	-	-		**1716.9**
CGA-205375	**2.79**	**0.022**	**2.6**	**0.179**	**8.36**[3]	**0.099**	**0.870**	**0.252**	**1.33**

[1] ECOSAR estimated chronic value is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC).
[2] Green algae
[3] Endpoint exceeds predicted water solubility of compound.
BOLD values are ECOSAR (v1.00) toxicity estimates (lowest toxicity value of multiple ECOSAR classes is shown, i.e., the most toxic).
Italic values are from submitted toxicity studies (most sensitive endpoint if multiple are available)
FW = freshwater and ME = marine/estuarine